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ABSTRACT

Included in this high school biology unit on sickle cell anemia are the following materials: a synopsis of the history of the discovery and the genetic qualities of the disease; electrophoresis diagrams comparing normal, homozygous and heterozygous conditions of the disease; and biochemical characteristics and population genetics of the disease. A list of filmstrips, pamphlets and books to be used as reference materials is given. Also appended are genetics problems and overhead projection materials mapping areas of the world in which sickle cell anemia and malaria are prevalent. (CS)

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sickle cell unit

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SE 029 959

Knowledge of some diseases causes people not to be as concerned about them as they might be. This type of thing has happened to sickle cell disease. Up until a few years ago almost no one had even heard of the disease let alone know anything about it. With the beginning of Black awareness and the desire to know about Black culture there has been an increase in the amount known by the general public concerning this ethnic disease. As knowledge about the facts of the disease increased also there was an increase in the understanding of the role that this condition had played in the evolutionary and ecological theaters.

From a historical standpoint it was Dr. James Herreck who first saw sickled hemoglobin and reported it in the early 1900's. The cover of this unit shows how the red blood cells looked that Herreck saw. The diagram below compares normal and sickled red blood cells (RCB's).

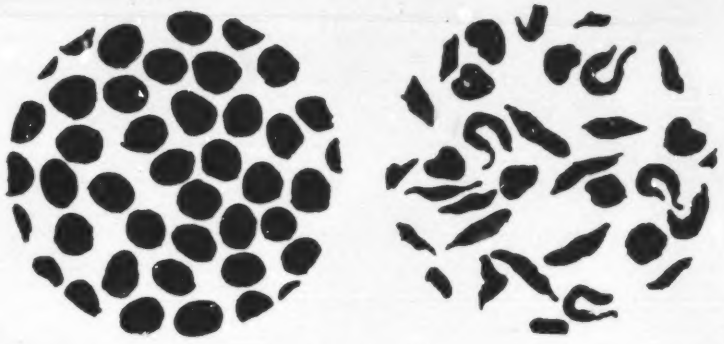

Figure 1. Graphic representation of RBC's with and without sickle hemoglobin. Normal is on the left.

It was not until the 1950's when a geneticist, J. V. Neel of the University of Michigan, reported that the disease was inherited as a simple Mendelian recessive trait. Prior to Neel's biological discovery, Linus Pauling at tht California Institute of Technology announced the discovery of electrophoretic activity in the sickle cell hemoglobin. Figure 2 on the following page shows the electrophoresis that Pauling discovered.

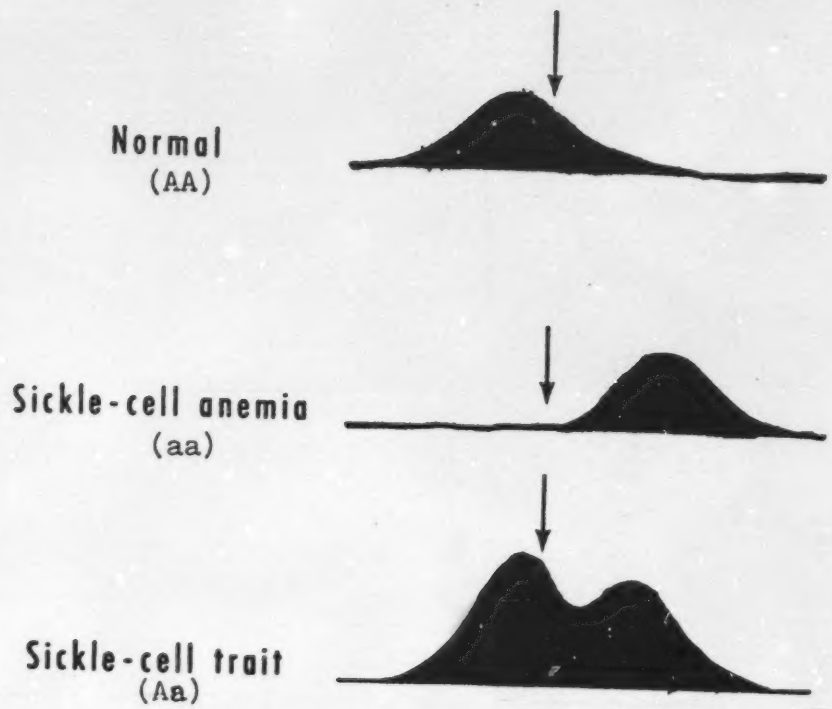

Figure 2
Pauling, Itano, et al reported in SCIENCE, 110:543-548, 1949 that the above patterns had been observed in the examination of the hemoglobin of the types of individuals named to the left. The genotypes are shown under the phenotypic descriptions.

The great milestone occurred in 1956 when Vernon Ingram at Cambridge University announced that he had discovered the molecular formula for hemoglobin.

Ingram's discovery led the way to analysis and in no time at all sickle cell disease was discovered to be a fault in the gene's transcription of amino acids. In hemoglobin there are 574 amino acids that must be placed at precise points. In sickle cell hemoglobin there is a substitution which occurs changing one amino acid (glutamic acid) for another amino acid (valine). This change occurs twice in the whole 574 acids which make

up the hemoglobin chain. It might be supposed that the substitution of so few elements would not make a significant difference in the end product but such is not the case. The major factor in understanding the sickling phenomenon comes from understanding the space relationships within the molecule. When valine is present, as in sickle cell hemoglobin, and oxygen is in short supply there is a tendency of the molecule to twist about the area where valine is located. This distortion is passed on to the red blood cell and the result is the familar sickled cell (see fig. 1). Murayama's hypothesis states that sickle cell hemoglobin when deoxygenated, polymerizes by means of hydrophobic interaction to form microfilaments and microcables which result in the distortion of the RBC.

Since these changes are visible it might be assumed that they would be observed and treatment start in infancy. Unfortunately such is not the case. In the study of human embryology and primary development there are five different hemoglobins. It is not until the third month following our birth does our "normal" hemoglobin become the dominant hemoglobin in our bodies. Prior to this time most of our blood cells and globin molecules were produced in the yolk sac, liver, or spleen. After birth most blood production switches to the bone marrow. It is in the marrow that the adult hemoglobin is manufactured. For a further discussion the reader should consult the chapter on "Hemoglobin Synthesis," in the book SICKLE CELL, by the Upjohn Company, pp. 13-14.

From the chemical standpoint the problem occurs when the microfilaments and microcables occur in such numbers to cause the blockage of the microcirculation. The disease sickle cell anemia occurs in two separate forms... one milder and less dangerous. There is considerable misunderstanding of the difference between having the disease and having the trait. The table on the following page will clear up the misunderstanding if it is studied carefully. Notice the phenotypic and genotypic aspects of the chart as well as the condition of the hemoglobin. Refer also to figure 2 on page 2.

NAME OF CONDITION	CONDITION OF HEMOGLOBIN	GENETIC SHORTHAND
normal	no sickling seen in hemoglobin	Hb^AHb^A
sickle cell trait	normally no sickling; can be induced when oxygen deprivation occurs	Hb^AHb^S
sickle cell anemia (disease)	sickling of cells generally fatal in early life-painful	Hb^SHb^S

Figure 3. Table comparing conditions noted in hemoglobins.

From this it is obvious that persons who have the trait only rarely show the effects of the disease since it must be induced by some type of anoxia. Even in those persons who are Hb^SHb^S there are other modifying situations- one of these is penetrance. Penetrance simply describes how strong a gene is. Expressivity is another possible modifier; this deals with how a gene shows itself.

Those persons who have African ancestors are those most concerned with passing the trait along to their children. It should be understood that this type of disease is NOT restricted to blacks. The table which is below shows the distribution of the Hb^S gene in various populations.

GROUP	INCIDENCE OF Hb^S (in %)
Equatorial African tribes	20% - 40%
Sicily & Greece	10% - 17%
American blacks	8%
India	6%
Northern Europeans	<1%

Figure 4. Incidence of Hb^S Gene in Various Populations

In patients with Hb^SHb^S who receive no treatment the fatality rate is nearly 100%. Since nature through certain developmental pathways(termed by some as the theory of evolution) has attempted to maintain the most variety with the least amount of death, it might be asked why has the Hb^S gene been so successful. The reason for this has been explained in the theory termed Balanced Polymorphism. It is this balance of one factor- survival from malaria vs another death from sickle cell anemia. The table below shows this idea of balanced polymorphism.

GENETIC CONDITION	EFFECTS	OUTCOME
Hb^AHb^A (normal)	afflicted with malaria	death
Hb^AHb^S (trait)	resists malaria	life
Hb^SHb^S (anemia)	dies from sickle cell anemia	death

Figure 5. Balanced Polymorphism

The ideas that are presented in the table above were first substantiated by the British Anthony Allison. The relationships between the malarial organism called Plasmodium falciparium and the Hb^S gene. The chart can be further substantiated using a population evaluation technique called the Hardy-Weinberg Law. This law states that genes continue in the same relative frequency within population unless they are acted upon by an outside force.

In the following exercise the following equivalents are given: $Hb^A = p$; $Hb^S = q$; $t = 0\%$ dying from malaria; $s = \%$ dying from sickle cell anemia.

PHENOTYPE	GENOTYPE	RELATIVE FREQUENCY	RELATIVE FITTNESS
normal	Hb^AHb^A	p^2	1-t
trait	Hb^AHb^S	2pq	1
anemia	Hb^SHb^S	q^2	1-s

Figure 6. Table Useful in Hardy-Weinberg Determinations Concerning Sickle Cell Gene Distribution

The proportion of total Hb^A alleles eliminated by reduced fittness in a malarial environment is defined as

$$\frac{tp^2}{p}$$

and likewise the proportion of Hb^S alleles eliminated by sickle cell anemia is

$$\frac{sq^2}{q}$$

In an environment allowing the use of the Hardy-Weinberg hypothesis it is noted that the two factors are at equilibrium.

$$\therefore \frac{tp^2}{p} = \frac{sq^2}{q}$$

$$\text{then } p = \frac{s}{s+t} \quad ; \quad q = \frac{t}{s+t}$$

Assume in nature Hb^SHb^S (q^2) is lethal {s=1} and that at equilibrium of malaria q=0.1.

*What is the relative fittness of the normal Hb^AHb^A (p^2) compared to Hb^AHb^S (2pq) ?

SOLUTION: Solving for t in the equation $q = \frac{t}{s+t}$

since q=0,1 and s=1

$$0.1 = \frac{t}{1+t}$$

$$\therefore t = \frac{1}{9}$$

relative fittness of $p^2 = 1 - \frac{1}{9}$

$$= \frac{8}{9} \qquad \text{and } 2pq = 1$$

*So the ratio is 9:8 in favor of Hb^AHb^S over Hb^AHb^A in a malarial environment.

In a nonmalarial environment the relative fittness would be changed so that normal would equal 1 (that is t=0). Since there would be removal of Hb^S alleles when combined homozygously there would be an increase of p^2 and a decrease of 2pq and the q (Hb^S) allele should eventually be eliminated from a nonmalarial region.

The interaction of Hb^S and malarial resistance stands as testimony to nature's attempt to sustain all types of life in varied habitats through all kinds of odds. The problem with anemia may be solved by man as he seeks to better understand what and why nature has behaved as she has.

To complete the study of this unit it is expected that you will watch the filmstrip, work the problems, do the labs suggested, and research and write a short newspaper-type article (limit to ca. 250 words.)

To assist you the following references are offered.
FILMSTRIPS:
"Sickle Cell...An Inherited Disease," Glenn Educational Films, Inc., P.O. Box 371, Monsey, N.Y. 10952. {East # 613.9-SIC}

BOOKS:
SICKLE CELL, The Upjohn Company, Kalamazoo, Michigan.

PHAMPLETS: (sources)
- Association for Sickle Cell Disease for Charlotte-Meck., 951 South Independence Blvd., Charlotte, N.C. 28202
- Center for Sickle Cell Anemia, Howard University College of Medicine, Washington, D.C. 20001
- National Association for Sickle Cell Disease, Inc., 945 South Western Ave., Suite 206, Los Angeles, Calif. 90006
- National Foundation-March of Dimes, P.O. Box 2000, White Plains, N.Y. 10602.
- U.S. Dept.HEW, NIH, Nat. Sickle Cell Disease Program, Bethesda, Md., 20014 {see verticle file East Media Center}

GENETICS PROBLEMS (EXTRA CREDIT)

In the following two genetics problems there will be an opportunity for you to achieve some extra credit on this unit. Use whatever resources you can to reach the correct answers. DO NOT HAVE THEM DONE BY SOMEONE ELSE.

1} In the United States about one Black out of 576 has a sickle cell anemia that can be distinguished by the sickled shape of the RBC when they are in a low oxygen concentration. This is due to a homozygous effect of the gene. Recently it has been found that the heterozygous carriers can be recognized by the formation of some sickle cells when the blood is held at a much lower oxygen concentration. In a certain southern city there are 60,000 Blacks. A research team sets out to determine how many of these have sickle-cell anemia and how many are heterozygous for the trait. How many would you expect to find in each group? (SHOW YOUR WORK)

2} After completing their examinations the research team actually finds that 90 persons have sickle cell anemia and that 5,410 carry the gene in the heterozygous state. Using the tabular method of finding chi-square, compare these two figures with the expected figures that were obtained in problem 1 and determine if anything but chance is operating to cause the difference. Refer to the table below and indicate what percentages of the cases would have deviations this great by chance alone. (SHOW YOUR WORK)

Chi-Square Numbers Arranged According to Chance Occurrence in Percentage

Degrees of Freedom	Possibility of chance occurrence in percentage (5% or less considered significant)								
	90%	80%	70%	50%	30%	20%	10%	5% (sig.)	1%
1	0.016	0.064	0.148	0.455	1.074	1.642	2.706	3.841	6.635
2	0.211	0.446	0.713	1.386	2.408	3.219	4.605	5.991	9.210
3	0.584	1.005	1.424	2.366	3.665	4.642	6.251	7.815	11.341
4	1.064	1.649	2.195	3.357	4.878	5.989	7.779	9.488	13.277
5	1.610	2.343	3.000	4.351	6.064	7.289	9.236	11.070	15.086
6	2.204	3.070	3.828	5.348	7.231	8.558	10.645	12.592	16.812
7	2.833	3.822	4.671	6.346	8.383	9.803	12.017	14.067	18.475
8	3.490	4.594	5.527	7.344	9.524	11.030	13.362	15.507	20.090
9	4.168	5.380	6.393	8.343	10.656	12.242	14.684	16.919	21.666

MALARIAL AREAS

SICKLE CELL AREAS

SICKLE CELL ANEMIA
TRANSPARIENCIES

In order to use the transparency masters the following procedure should be followed:

1. Use the blank map of the SICKLE CELL vs MALARIA and make a base cell using thermofax or other process.
2. If other color thermal film available make overlays using the other masters. If no other color films available use black for one and then color in the other using projection pen.
3. If no thermal process is available the same result can be obtained using clear film and a projection pen or grease pencil.
4. The flowers and the "+"'s are to help in the alingment.

+ SICKLE CELL ❋

VS

MALARIA ❋

+